The Influence of Inhaled Nitric Oxide on Cerebral Blood Flow and Metabolism in a Child with Traumatic Brain Injury

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Case Report

We present a 10-yr-old girl after a motor vehicle accident (Glasgow Coma Scale score 4T) with acute respiratory syndrome, pulmonary hypertension (PHTN), and diffuse axonal injury and a subarachnoid hemorrhage in whom middle cerebral artery blood flow velocities (Vmca), jugular bulb saturations (SjO_2), and intraparenchymal intracranial pressure (ICP) monitoring were used to guide treatment with inhaled nitric oxide (INO).

During the first 24 h of intensive care unit admission, the patient's ICP was 25–30 mm Hg despite hyperventilation ($Paco_2$, 30–35 mm Hg), mannitol therapy (serum osmolality, 310 mosm/kg), and sedation with lorazepam (20 $\mu g \cdot kg^{-1} \cdot h^{-1}$). Despite treatment with IV phenylephrine (1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), dopamine (30 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and epinephrine (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$), it was difficult to sustain a cerebral perfusion pressure of at least 60 mm Hg. Pulmonary artery catheter findings were used to differentiate between right and left heart failure. On hospital day 2, trans-thoracic echocardiogram revealed a torn anterior tricuspid valve leaflet with wide-open tricuspid regurgitation, PHTN, and biventricular dysfunction. There was no atrial shunting. Right and left ventricular ejection fractions were 19% and 30%, respectively. Right and left ventricular failure was presumed to be attributable to PTHN and resultant septal wall motion, respectively. PHTN was treated with hyperventilation, which decreases ICP. Epinephrine was discontinued to avoid an increase in afterload; IV dobutamine was administered to increase cardiac output. To assess cerebral oxygen delivery and extraction and to guide the degree of hyperventilation (ICP, 25–30 mm Hg), we placed a retrograde jugular bulb catheter via the right internal jugular vein on hospital day 3.

On hospital day 4, approval for administration for INO for treatment of PHTN was obtained. Bilateral Vmcas were insonated by using transcranial Doppler during the INO trial. INO was administered via the tracheal tube starting at 5 parts per million (ppm) and titrated in increments of 5 ppm to a maximum of 35 ppm at 10-min intervals (Table 1). The optimal dose of INO was to be determined by identifying the dose beyond which an increase in INO caused no further decrease in peripheral vascular resistance (PVR), a decrease in systemic blood pressure, or an increase in Vmca, ICP, or SjO_2. At INO 10 ppm, PVR and mean pulmonary artery pressure decreased significantly and cardiac index improved. An increase in INO from 10 ppm to 35 ppm resulted in no further decrease in PVR. However, we observed an increase in systemic vascular resistance (SVR) and mean arterial blood pressure (MABP) with an increasing dose of INO; the SVR decreased with a taper to 10 ppm while the MABP remained increased (154 mm Hg). As a result, INO was discontinued shortly thereafter. The return of MABP to normal occurred after 15 min. There were no clinically significant changes in Vmca, SjO_2, or ICP during the nitric oxide (NO) trial (Table 1). The patient was transferred to a rehabilitation facility on hospital day 14 (Glasgow Outcome Scale score, 4).

Discussion

It has been suggested that NO exerts an influence on basal cerebrovascular tone and stimuli mediated tone (inducible form) in both conscious and anesthetized states (1–3). The mechanism of NO induced vasodilation involves cyclic guanosine monophosphate and a decrease in intracellular calcium, but there is evidence to suggest that the NO-associated increase in cerebral blood flow (CBF) is unrelated to an increase in cerebral metabolic rate (4). In neurologically intact animals with PHTN, INO did not show any adverse effect on CBF; our findings corroborate these observations (5–7). The contribution of NO to cerebral vasodilation during hypercapnia, hypoxia, and autoregulation is uncertain. Although Iadecola (8) and others have demonstrated that increases in CBF resulting from hypercapnia are inhibited by NOS inhibitors, suggesting that NO plays an important role in the cerebral vascular response to CO_2, others investigators failed to confirm this (8–10). Increases in CBF during hypoxia and decreases in CBF during hypocapnia are altered by inhibitors of NOS (11–14). Although earlier studies show no effects of NO on cerebral autoregulation, Jones et al. (14) describe increases in the lower limit of autoregulation with NOS inhibitors.

This report is of value because there are no data about the cerebrovascular effects of INO in humans

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Table 1. Patient Data During Inhaled Nitric Oxide (INO) Administration

Time (min)	5	15	25	35	45	55	65	75	85
INO (ppm)	0	5	10	15	20	25	30	35	10
PVR (d/cm^2)	600	278	154	170	209	200	274	275	193
MPAP (mm Hg)	28	28	24	26	27	29	28	28	28
SVR (d/cm^2)	2000	2010	2006	2018	2208	2331	2711	2715	2234
CI (L/min/m^2)	1.4	2.1	2.6	2.6	2.4	2.6	2.3	2.4	2.5
MABP (mm Hg)	102	108	110	110	117	117	116	133	146
Vmca L (cm/sec)	119	128	121	119	116	115	110	118	123
Vmca R (cm/sec)	106	108	103	100	100	99	94	103	114
ICP (mm Hg)	23	21	23	22	22	22	21	21	23
Sjo_2 (%)	79	82	82	82	81	80	81	82	84
Svo_2 (%)	65	78	79	79	78	78	78	80	84
Pao_2 (mm Hg)	77	136	146	151	157	168	155	152	154
$Paco_2$ (mm Hg)	34	34	33	33	34	33	34	34	34
pH	7.41	7.41	7.41	7.42	7.42	7.43	7.43	7.43	7.42

PVR = peripheral vascular resistance; MPAP = mean pulmonary arterial pressure; SVR = systemic vascular resistance; CI = cardiac index; MABP = mean arterial blood pressure; Vmca L = left middle cerebral artery blood flow velocity; Vmca R = right middle cerebral artery blood flow velocity; ICP = intracranial pressure; Sjo_2 = jugular bulb saturation; Svo_2 = venous oxygen saturation; Pao_2 = partial pressure of arterial oxygen; $Paco_2$ = partial pressure of arterial carbon dioxide.

with traumatic brain injury (TBI). We used transcranial Doppler and SjO_2 monitoring during the INO trial because administration of INO could have adversely increased CBF and ICP. Although SjO_2 alone could have been used as an indirect measure of CBF, we could not have differentiated whether changes in SjO_2 would be the result of an increase in CBF (hyperemia) or a decrease in cerebral metabolic rate of oxygen. Similarly, measurement of Vmca alone would not have allowed us to assess the influence of changes in cerebral metabolic rate. The use of ICP monitoring alone does not identify the etiology of increased ICP. Although there was an increase in SjO_2 with increasing doses of INO, it was small and there was no change in ICP. The lack of adverse cerebrovascular effects of INO in our patient may be because it is metabolized before it reaches the cerebral circulation. It is also possible that in patients with TBI and hyperemia, cerebral vessels are maximally vasodilated or in a state of vasoparalysis because of endogenous NO, and hence they are unresponsive to exposure to additional exogenous NO (15). Within the range of MABP studied, Vmca and ICP did not increase; this is indirect evidence of intact cerebral autoregulation.

Short-term hyperventilation is commonly used to treat PHTN in the emergent setting when other treatment modalities are unavailable but hyperventilation for the treatment of PHTN associated with acute respiratory syndrome may increase the risk of lung injury (16). Additionally, the use of hyperventilation in this patient was complicated by the concern for cerebral ischemia. The interaction of hyperventilation with INO may have masked the intrinsic cerebrovascular effects of INO. Further studies of these interactions are indicated.

The reason for the apparent increase in SVR and MABP remains unclear. We excluded inadequate analgesia, a change in stimulation, or vasopressor effect as a cause of systemic hypertension. The parallel decrease in SVR with INO taper to 10 ppm suggests an association between INO and SVR. We speculate that a sudden decrease in PVR led to cardiac conformational changes and an idiosyncratic increase in SVR and MABP.

In conclusion, this is the first report of the cerebrovascular effects of INO in a patient with TBI. Although we report a decrease in PVR and an idiosyncratic increase in SVR, we report no clinically significant changes in Vmca, SjO_2, or ICP during the INO trial. Our observation is important because it suggests that inhaled NO might be safe for administration in some patients with TBI and hyperemia. We found transcranial Doppler, SjO_2, and ICP monitoring to be complimentary and useful monitors during the INO trial.

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